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Host-Pathogen Protein-Protein Interaction Prediction Using an *in silico* Model

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Summary and Implications

Newcastle Disease (ND) is caused by Newcastle Disease Virus (NDV) and is a major problem in developing countries where vaccination against NDV is not easily achievable. A step required for NDV infection is the cleavage of the NDV fusion (F) protein. Using structural information of the NDV F protein and the only known host protein binding partner, protein disulfide isomerase A3 (PDIA3), we computer modeled the interaction between the two proteins by looking at a docked structure of these two proteins. With our docked structure, we visualized one of the catalytic domains of PDIA3 being near the cleavage site of the NDV F protein. We also discovered a novel binding pocket on the NDV F protein that interacts with the second catalytic domain of PDIA3. This new insight may provide additional molecular targets for NDV vaccine development.

Introduction

Newcastle Disease is an avian disease with major global impact, especially in developing countries where the virulent strain is endemic. Up to 80% of chickens die within days of infection by a high virulence strain. Unfortunately, this spells trouble for poor rural families that rely on their flock for protein and income. ND is caused by NDV, and vaccines for ND are available in developed countries. Of the little that is known about the mechanism of NDV infection, the cleavage of NDV F protein is a crucial step during the virus invasion of the host cell. In 2014, chicken PDIA3 was found as the first host binding partner for NDV F protein. In this study, we used an *in silico* method to visualize the docking of NDV F protein to the chicken PDIA3 in order to confirm the potential activation of the NDV F protein by PDIA3.

Materials and Methods

The NDV F protein and PDIA3 protein structures were downloaded from Protein Data Bank (PDB). PDB's NDV F protein was a partial tertiary (3D) structure missing information at the cleavage site, and PDB's PDIA3 tertiary structure was that of human. Using SWISS-MODEL, we predicted the complete structure of NDV F protein and chicken PDIA3 based on the PDB structures. The predicted structures were inputted into two protein docking software programs, ClusPro 2.0 and ZDOCK 3.0.2, to generate docked structures of chicken PDIA3 bound to NDV F protein. Finally, PyMOL 1.7.6.6 was used to visualize and explore a detailed docked structure generated by ClusPro.

Results and Discussion

The predicted structure of chicken PDIA3 by SWISS-MODEL had high accuracy due to the high similarity of PDIA3 amino acid sequences between human and chicken. On the other hand, the predicted structure of the complete NDV F protein was not as good due to the fact that the missing part of the PDB structure is in a loop–an inherently unstable structure. Despite the shortcomings of the predicted NDV F protein structure, ZDOCK's top 500 docking results showed dramatic improvement in the docking structure prediction accuracy using SWISS-MODEL structures over PDB structures.

One of the predicted PDIA3/NDV F protein docking structures by ClusPro (Figure 1a) had an especially good score based on multiple metrics. The structure shows the attachment of the PDIA3's 2 catalytic domains to the head region of the NDV F protein. One of the catalytic domains is near the cleavage site of the NDV F protein. This strongly suggests that PDIA3 is directly involved in the activation of the NDV F protein. The other catalytic domain is shown to be surrounded by a novel binding pocket (Figure 1b) formed by 11 residues (Figure 1c) on the NDV F protein. This novel binding pocket on the NDV F protein has enormous implications for vaccine development. Currently, the development of vaccines has focused on the known cleavage site, and the available vaccines have been difficult to distribute in developing countries. The new molecular targets on the novel binding pocket can lead to development of new vaccines to help reduce the negative impact of NDV infections.

Acknowledgments

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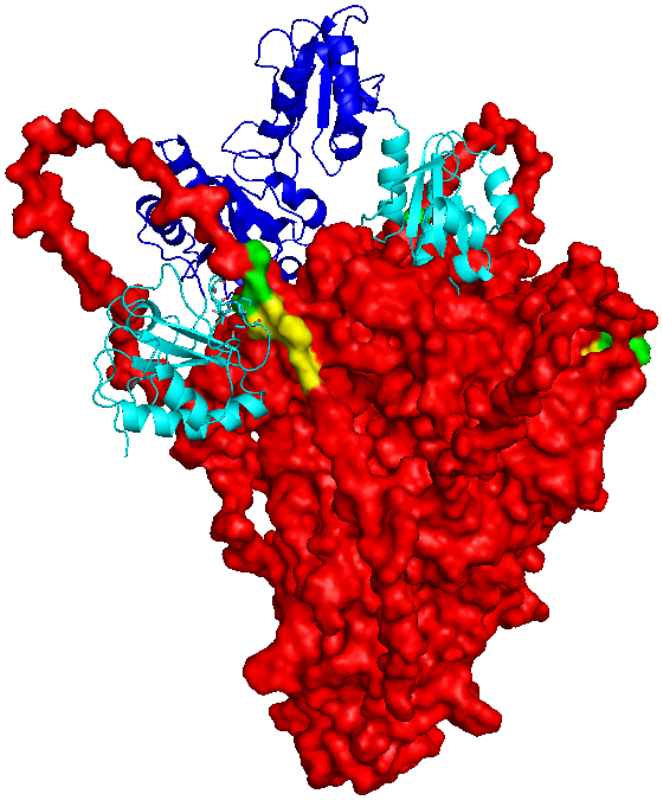
Figure 1. Predicted docking structure of chicken PDIA3 and NDV fusion (F) protein. (A) The side profile view of the entire structure of chicken PDIA3 (blue) with the catalytic domains highlighted (cyan) docked to NDV F protein (red) with the cleavage site highlighted (green and yellow). Note that the model predicts the PDIA3 catalytic domains binding to the cleavage site and a novel binding pocket on the NDV F protein. (B) A zoomed in view of the 4 chicken PDIA3 catalytic residues surrounded by the novel binding pocket formed by NDV F protein residues. (C) A simplified view showing the interacting residues on the NDV F protein as predicted by the docked structure. A total of 11 residues were predicted to be within close proximity to the 4 catalytic residues on the chicken PDIA3.

A



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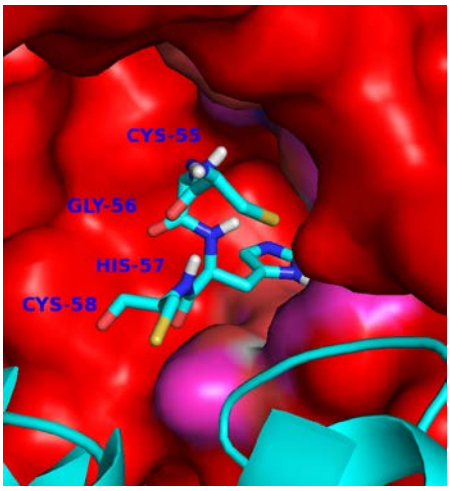

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